REMARKS/ARGUMENTS

1. Remarks of the Amendment

The present application originally contained Claims 1-43. Applicant elected to prosecute Claims 1-29 and cancelled Claims 30-43 in a Response to Requirement For Restriction dated April 20, 2000. Claims 9 and 22-23 were cancelled by Amendment dated April 24, 2002.

Claims 3-5, 10, 13, 15-21 and 24-29 were cancelled without prejudice by Amendment After Final dated November 15, 2002 for the sole purpose to reduce the rejections to a single issue for consideration by the Examiner.

Currently, Claims 1, 2, 6-8, 11, 12 and 14 are pending. All claims are method claims, and only Claim 1 is presented in independent form. Claim 1 has been amended to more specifically define Applicant's claimed invention. Antecedent basis for the amendment to Claim 1 is found in the Specification, page 4, lines 9-13.

2. Response to the Rejections of Claims 1, 2, 6-8, 11, 12 and 14 Based Upon 35 USC §112, first paragraph – New Matter and Written Description

Claim 1, 2, 6-8, 11, 12 and 14 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner contends that the specification does not support the further limitation of the scope of the invention of a promoter which is active only in progenitor cells of red blood cells. Therefore, the Examiner alleges that this claim limitation is new matter.

The Examiner further contends that the specification does not provide a written description of a genus of promoters that are active only in progenitor cells of red blood cells. Therefore, the Examiner further alleges that Applicant was not in possession of the claimed invention at the time of filing.

These two rejections are obviated by the amendment to Claim 1 wherein th claim is limit d to a globin promoter. More specifically, Applicant has limited the

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scope of the promoter to be a globin promoter which is active only in only in progenitor cells of red blood cells. In addition, the claim limitation of a globin promoter obviates the rejection relating to the Examiners contention that Applicant failed to disclose a genus of promoters that are active only in progenitor cells of red blood cells.

Applicants respectfully point out that Applicant is entitled to limit the claim to a globin promoter because in the Specification, page 4, lines 9-13, Applicant equates a hemoglobin promoter as a globin promoter. Moreover, the Examiner twice recognizes in the present rejection that the hemoglobin promoter is a globin promoter. Still further, one skilled in the art would know at the time of the invention that the globin promoter is active only in only in progenitor cells of red blood cells. Therefore, Applicant is entitled to limit the claim to a globin promoter.

Accordingly, Applicant respectfully requests withdrawal of the rejections based upon 35 USC §112, first paragraph, New Matter and Written Description

3. Response to the Rejections of Claims 1, 2, 6-8, 11, 12 and 14 Based Upon 35 USC §112, first paragraph – Enablement

Claim 1, 2, 6-8, 11, 12 and 14 stand rejected under 35 U.S.C. §112, first paragraph. Applicant's representative is surprised that the Examiner withdrew the finality of the previous Office Action and now asserts to be "exploring" 35 USC 112, first paragraph issues because this is the fifth office action in which 35 USC 112, first paragraph issues are being considered while the issues raised in the four prior office actions having been resolved. The prolonged prosecution by the Patent Office is not merited and this rejection appears to wonder through the prior art only to arrive at a place that was previously considered.

Essentially, the Examiner contends that the specification does not enable one skilled in the relevant art to make and use the claimed invention. First, the Examiner considers the scope of cells, vectors and promoters that can b used to make the claimed invention and th n the Examiner reverts to the previous

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considered issue of therapeutic use of the claimed invention. For example, the Examiner states "Most non-replicating episomal vectors are lost during clonal expansion, thus adenovirus and herpes virus vectors, embraced by the instant claims, are not suitable for long term modifications of hematopoietic tissue such as would be required for the therapeutic applications...." In addition, the Examiner raises questions about efficiency, sustained production, etc. for use in gene therapy. Therefore, Examiner contends that the claimed invention encompasses gene therapy and is not enabled by the present specification. This rejection is respectfully traversed.

The dispositive issue in the present application is "What is the claimed invention?" Applicant maintains that as defined, the present claimed invention is a method for producing and delivering protein in vivo. More specifically, the method comprises inserting into a vector a globin promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is non-native to red blood cells, wherein said promoter and said gene are operably linked; collecting an amount of progenitor cells of red blood cells from a mammal; transfecting said progenitor cells of red blood cells in vitro with said vector containing said promoter and said gene; introducing the transfected progenitor cells of red blood cells back to said mammal, wherein the transfected progenitor cells of red blood cells produce altered red blood cells containing said protein which is non-native to red blood cells in vivo in said mammal, and wherein said protein which is non-native to red blood cells is contained only in said altered red blood cells, and thereafter said protein which is non-native to red blood cells is released into a bloodstream of said mammal through rupture of said altered red blood cells.

Applicant's claimed invention is not a method of using proteins produced in vivo to treat diseases. Furthermore, although the present invention can be used for facilitating disease treatment as apparent to one skilled in the art, Applicant claimed invention as defined by the claims is not, nor ever intended to be, a gene therapy method.

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Whether a claim is enabled under 35 U.S.C. 112, paragraph 1 is a question of law, although based upon underlying factual findings. See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ 2d 1618, 1623 (Fed. Cir. 1996); In re Goodman, 11 F.3d 1046, 1049-50, 29 USPQ 2d 2010, 2013 (Fed. Cir. 1993).

The first paragraph of 35 U.S.C. 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The present rejection is based upon the Examiner's definition of what subject matter is encompassed by the claims and not on the Specification and plain meaning of the claim words. The Examiner has attempted to expand the claims to encompass gene therapy because it is mentioned in the Specification. However as held in Raytheon Co. v. Roper Corp, 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), *Cert. Denied*, 469 U.S. 835 (1984), "That claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims."

The Examiner has failed to point out any particular claim elements, which are broader than a method of producing a protein only in the progenitor cells of red blood cells, and delivering produced protein into bloodstream by rupture of the red blood cells such that the claim is not enabled. Enzo Biochem Inc. v. Calgene Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129 (Fed. Cir. 1999).

In addition, the Examiner has failed to point out any inconsistency in the plain meaning of the claim terms to indicate that the claim terms are broader than a method of producing a protein only in the progenitor cells of red blood cells, and delivering produced protein into bloodstream by rupture of the red blood cells such that the claim t rms are not nabled. National Recovery Techs., Inc. v. Magnetic

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Separation Sys., Inc., 166 F.3d 1190, 1194, 49 USPQ2d 1671, 1674 (Fed. Cir. 1999).

Applicant is only responsible for enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims. As Examiner previously stated on page 4, line 6 of the first Office Action, the present invention is "enabling for delivery of a protein to the blood in vivo". That is precisely the claimed invention. Now however, the Examiner has consistently withdrawn from this position in order to support his enablement rejection for gene therapy.

To support his enablement rejection, the Examiner finds that the claims encompass non operative embodiments on the basis of the prior art and therefore believes this factor should be fatal to granting allowance to the claimed invention. However, Applicant respectfully points the Examiner's attention to the well settled proposition that the mere possibility a composition claim embraces inoperative species or a process claim embraces inoperative reactants does not render it unduly broad. In re Kamal et al. (CCPA 1968) 398 F2d 867, 158 USPQ 320; Ex parte Crouch (POBA 1952) 97 USPQ 461; Ex parte Friedman (POBA 1962) 136 USPQ 381; In re Sarett (CCPA 1964) 327 F2d 1005, 140 USPQ 474; Ex parte Clark et al. (POBA 1971) 17 USPQ 40. Moreover, as clearly stated in In re Cook, 169 USPQ 298, 302 (C.C.P.A. 1971) (quoting In re Skrivan, 166 USPQ 85, 88 (C.C.P.A. 1970))

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit "factors which must be presumed to be within the level of ordinary skill in the art," . . . and therefore read on embodiments in which such factors may be included in such a manner as to make the embodiments inoperative. There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such manner as to make the embodiment op rative rather than inoperative. . . . The word "obvious" as

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here used means that those skilled in the art would know how to determine utility without having to build and try out the conceived embodiment and could do so without the expenditure of unreasonable effort.

Therefore, Applicant maintains that in spite of the fact that specific cells, vectors and promoters are not provided with detailed specificity, their choice is readily apparent from the prior art without undue experimentation. For example, it is readily determined from a reference cited by the Examiner, Rivella et al (Seminars in Hematology 35(2):112-125 at page 122, first column (1998)) that the minimal LCR merely acts as an erythroid-specific enhancer. This having been known, Applicant further limited the claimed invention in Claim 2 to the inclusion of an enhancer.

The Examiner cites Teitz et al (DNA and Cell Biol. (Jul 1994) 13(7):705-710 and J. Pathol. (1995 Nov 177(3) 309-15) for the proposition that because the mice developed soft tissue sarcomas it was clear evidence that the expression of a gene under the control of a globin promoter was not restricted to erythroid cells.

Applicant believes that the Examiner is stretching the 1994 reported observations of Teitz and diminishing the 1995 reported observations of Teitz as well as observations from others. Although the 1994 reference concludes that the work supports the observation that μ LCR in combination with the T antigen gene triggers the appearance of sarcomas, it also states that the DNA sequences *may* (emphasis added) bind specific muscle transcription factors and the triggering sarcomas is *likely* (emphasis added) connected to its ability to inactivate p53, in comparison with the conclusions of the 1995 reference which finds "Possibly, there is a random low-probability activation of the transgene in a few cells, such as from point mutations, changes in methylation, or amplification, which then become transformed. Alternatively, there may be a second hit at a different locus, whether genetic or epigenetic, which allows Tag expression. In addition, other events besides Tag expr ssion are presumably required for the malignant transformation." Consequently, Teitz is speculating on the reason for th sarcomas.

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Moreover, as reported in NewScientist.com, "'Miracle' gene therapy trail halted" (http://www.newscientist.com/news/news.jsp?id=ns99992878) (copy enclosed) boys with X-SCID (Severe Combined Immunodeficiency) have a faulty copy of a gene on their X chromosome that makes an immune protein called interleukin-2 and were treated by gene therapy. It was further reported that one out of a total of 15 patients developed leukemia. More specifically, the patient underwent gene therapy at the age of six months, and contracted chicken pox at two-and-a-half. The patient's white cell count increased in response to the infection, as would be expected, but his bone marrow then started uncontrollably producing these cells. The gene therapy involved shuttling the gene into the patient's cells using a harmless virus. But transferred genes cannot be targeted to insert into a specific part of a chromosome, and it appears, scientists say, that in this patient, the new gene was inserted next to an oncogene, called Lmo2, triggering the leukemia.

Accordingly, there are reasons to believe that there are other events required for a malignant transformation and consequently there is no clear evidence that expression of a gene under the control of a globin promoter would not be restricted to erythroid cells. Moreover, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC 112, first paragraph. Staehelin v. Secher, 24 USPQ 2d 1513, 1516 (B.P.A.I. 1992). It has been consistently held that the first paragraph of 35 USC 112 required nothing more than objective enablement which Applicant has met given the scope of the claimed invention. It is also well settled law that in satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art. How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 USC 112. Staehelin v. Secher, ibid.

Applicant intentionally avoided the therapeutic enabling issue by employing an approach that has been readily accepted, as shown in the primary reference,

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Hollis et al., which was used by the Examiner in further claim rejections. In the Hollis et al. reference, as well as, other protein expression patents, each uses the same strategy of claiming the expression or production of proteins rather than a specific gene therapy protocol. For example, Hollis et al recites purification of recombinant proteins. Still others adopt similar ways to claim either expression or production of proteins rather than the gene therapy for which the proteins would be used. Applicant has adopted this same approach by claiming the production and delivery of proteins rather than a method how to use the produced protein for the purpose of gene therapy. Gene therapy itself is a separate and very complex scientific subject that needs to be specifically addressed depending on each specific disease, organ involved and protein intake mechanism involved, regardless how the desired protein is produced.

Applicant has never claimed gene therapy. In fact, in the Background of the Invention, Applicant pointed out that gene therapy comprises many components necessary to obtain a specific gene therapy and each component has many variables. Therefore, it is apparent to the Applicant, the Examiner and those skilled in the art that each component, as well as, the precise gene therapy protocol would be new inventions. However, using the Examiner's unduly expanded interpretation of the claims, the Examiner is in effect denying Applicant's ownership of the claimed method of protein production and delivery just because the method can potentially be used in a therapeutic procedure. More specifically, if a precise gene therapy protocol was invented which uses Applicant's claimed protein production and delivery method, then the Examiner's position denies Applicant's inventive rights to Applicant's claimed invention. It is untenable of the Patent Office to refuse granting Applicant a patent on Applicant's discovered method merely because the discovered method is susceptible of further uses. It would be patently unjust to require an Applicant to delay seeking patent protection on one method of protein production and delivery until after a specific gene therapy has been discovered and has proven clinical use.

The Examiner's subjective view is not consistent with objective views that

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Applicant's claimed method of protein production and delivery is separate from an invention directed to the use of the protein in a gene therapy method. It is readily understood that a process to make a product is separate from a process to use the product for a specific purpose. Applicant believes that the present situation can be analogous to Applicant claiming a method of producing time-release high potency Vitamin C tablets, but Applicant would not be responsible for any clinical use of the Vitamin C for treatment of diseases. Consequently, Applicant maintains that Applicant should not be required to provide an enablement for the separate invention of gene therapy.

The Examiner's rejection is simply unfair and not logical to promoting the useful arts. Applicant maintains that he has complied with the requirements of 35 U.S.C. §112, first paragraph. Applicant's claimed invention has utility for producing and delivering proteins in vivo. The present Specification, page 6, provides a host of utilities for Applicant's claimed invention. More specifically:

> One object of the present invention is to provide a non-tissue specific method that utilizes suitable host cells for synthesis of proteins.
>
> Another object of the present invention is to specifically control the expression and production of proteins in the precursors of the red blood cells.
>
> An additional object is to utilize the non nucleated cell nature of the red blood cells to provide an environment that benefits the stability of the proteins after their production.
>
> Yet another object of the present invention is to bypass the secretion and exocytosis pathways for protein release from the manufacturing site.

Even given these utilities, the Examiner argues that none of them provide "reasons" for in vivo production and delivery of prot ins as claimed and r quires that

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"the specification must enable the practice of gene therapy of the broad range of disease set forth in the specification." However as previously cited, Raytheon Co. v. Roper Corp, *ibid*, holds that claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims.

Moreover, even though the claimed invention has potential utility in gene therapy, Applicants should not be required to enable gene therapy. For example, the fact that a valve is used in an instrument does not mean that a claim of a new method of making the valve must be accompanied with an enabling disclosure of how to make the instrument. All that is required is that the method of making the valve be described and enabled.

As previously mentioned, the Examiner initially indicated that the invention was enabling for the production and delivery of protein in vivo. But now, the Examiner has not provided any reason why the claimed invention is not separately enabled for the production and delivery of protein in vivo, except that the claimed production and delivery of protein in vivo can be used in gene therapy and gene therapy is not enabled by the specification. Applicant maintains the two are separate in nature and should not be construed as one invention. Applicant is only obligated to enable the claimed invention but not the other.

Notwithstanding the inappropriateness of the Examiner's reasoning of the rejection of the claimed method on the basis of lack of enablement for the specific use of the product produced for gene therapy, Applicant presents additional information to overcome the enablement rejection by demonstrating that in vivo production of protein has utility beyond gene therapy. In re Eynde, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973)

For example, it is known to one skilled in the art at the time of filing of the instant application that a protein produced in mammals can be harvested, purified, and then used as a protein supply for medical treatment in a similar manner to a medication, which is outside of the scope of gene therapy. In the present case, the mammalian body wherein the protein is produced in vivo, and delivered to a convenient harvesting site, for instance the bloodstream, is utilized as a "bioreactor"

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for manufacturing a desired protein which otherwise is difficult to obtain by other means.

A suitable example of bioreactor protein production is the production of human Alph-1 antitrypsin (AAT) in transgenic animals for treating AAT deficiency patients. AAT is a protein normally made in human liver. From the liver, AAT is released into the bloodstream, to travel to the lungs where it protects lung tissue from the harmful effects of neutrophil elastase. AAT deficiency is an inherited disorder. Because the AAT deficiency patients lack the ability to produce sufficient AAT, or not produce it at all, it can lead to emphysema at a young age.

Pharmaceutical Proteins Limited (PPL), Edinburgh, United Kingdom, demonstrated in early 1990 that human AAT can be produced with an adequate yield in transgenic sheep and harvested from the milk of these animals. The human AAT purified from the milk of these transgenic animals has biological activity indistinguishable from human plasma derived material *(Biotechnology (NY) 1991 Sept., 9(9):830-4)*. PPL Therapeutics and Bayer Corporation later launched clinical trials, which used the AAT produced by transgenic sheep to treat AAT deficiency patients (www.bayerbiologicals.com). The AAT in an aerosol formulation is delivered directly to the patients' lungs via an inhalation system. In another application, PPL also concluded its Phase II clinical trial in November 1998 for using three dosages of AAT to treat cystic fribrosis patients (www.ppl-therapeutics.com).

It is apparent that using the method of Applicant's claimed invention the AAT protein can be produced in the red blood cells via the control of the hemoglobin promoter and delivered into blood stream in a human body. However, using the method of Applicant's claimed invention human AAT protein can also be produced in the red blood cells and delivered into the bloodstream in sheep or other mammals, and then harvested and used as a protein supply for medical treatment of AAT deficiency patients, in a similar manner to PPL Therapeutics' approach. The difference between PPL Therapeutics' method and Applicant's claimed invention is in the method of in vivo protein production. PPL Therapeutics uses transgenic animals to produc the protein in mammary glands and

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Applicant's claimed method uses a non-transgenic animal to produce the protein in red blood cells of the mammal.

Applicant respectfully points out that Applicant's claimed invention is a method of producing and delivering protein in vivo, not how to use the produced protein. Gene therapy is only one possible approach to utilize the produced protein. It is important to understand that the protein produced by Applicant's claimed method can be utilized by means other than gene therapy.

Therefore, Applicant maintains that the pending application is in compliance with the requirements of 35 U.S.C. §112, first paragraph.

It is respectfully submitted that Claims 1, 2, 6-8, 11, 12 and 14, the remaining pending claims, are now in condition for allowance and such action is respectfully submitted. Applicant's Agent respectfully requests direct telephone communication from the Examiner with a view toward any further action deemed necessary to place the application in final condition for allowance.

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